REMARKS

The Applicants respectfully request reconsideration of the application, withdrawal of all rejections, and allowance of the claims in view of the following remarks.

I. Introductory Remarks

In response to the most recent restriction requirement, the Applicants elected, with traverse, the claims of Group III, e.g., claims 12 and 37-51, drawn to a method of treatment for hereditary lymphedema via VEGF-C gene therapy. The Applicants also elected the VEGFR-3 polymorphism at position 1114. All of the claims of Group III are believed to be generic relative to the elected polymorphism, including previously withdrawn claim 39, which has been amended to include the elected species, making it a linking claim. The subject matter of original claim 39 is now the subject of new claim 52.

The Applicants acknowledge with thanks the Examiner's confirmation that the polymorphism constituted a species election with the possibility of additional species being included upon allowance of a generic claim. Still, the Applicants dispute the characterization that the claims "encompasses missense mutation at multiple codons." The elected claims should be regarded as encompassing *methods of treatment*. The Patent Office routinely examines claims that specify treatment of patients with a disease in the generic sense, without requirement of an election as to the genetic mutations that contribute to the disease in the patient in need of treatment. To permit claims commensurate with the invention, the election of species should be withdrawn.

Many of the claims drawn to non-elected inventions have been canceled without prejudice, in view of the restriction and to minimize fees due for the new claims, and not for reasons related to patentability.

All of the amendments find basis in the application as originally filed.

For example, the limitations introduced into claim 12 find support in previously presented dependent claims (e.g., claim 37 or canceled 46). Claim 37 has been amended to read as an independent claim and specifies an affirmative screening step to identify the patient for treatment in the "administering" step. Such screening finds support

throughout the application (see, e.g., pp. 4-5) and is related to the subject matter of parent U.S. Patent No. 6,764,820.

Many dependent claims were amended to depend alternatively from either claim 12 or claim 37.

Amended claims 47-49 and new claims 53-61 specify additional characteristics of the VEGF-C gene therapy product. These claims find support throughout the application, including at pp. 14-18 and 25-27.

The Applicants reserve the right to pursue the subject matter of any claim as previously filed in a related application, such as a continuing application.

II. The "written description" rejection under 35 USC §112 should be withdrawn.

Pages 5-8 of the Office action set forth a rejection alleging inadequate written description of the claimed invention. The Applicants respectfully traverse.

A. A proper written description analysis focuses upon the claimed invention.

The written description requirement focuses on the invention that is actually claimed in the patent application. See, e.g., *Vas-Cath*, cited by the Patent Office at page 7 of the Office action. The elected claims are directed to a method of treatment of a subjects with hereditary lymphedema with a therapeutic agent. As such, the written description analysis should evaluate whether the claimed method of treatment is adequately described.

B. "VEGF-C gene therapy products."

The Patent Office alleged that there is inadequate description for "VEGF-C gene therapy products" as recited in the claims, asserting that the claims encompass VEGF-C analogs, including variants and fragments of SEQ ID NO: 4 (wild-type VEGF-C) that do not have VEGFR-3 stimulatory activity. The Applicants dispute this analysis. The very section of the application quoted in the office action by the Patent Office speaks of analogs "wherein the VEGFR-3 stimultory biological activity has been retained." The summary of invention

also specifies that the polypeptides and encoding polynucleotides for use in the invention have VEGFR-3 stimulatory activity:

> For the practice of methods of the invention, the term "VEGF-C polypeptide" is intended to include any polypeptide that has a VEGF-C or VEGF-C analog amino acid sequence (as defined elsewhere herein in greater detail) and that is able to bind the VEGFR-3 extracellular domain and stimulate-VEGFR-3 signaling in vivo. The term "VEGF-C polynucleotide" is intended to include any polynucleotide (e.g., DNA or RNA, single- or double-stranded) comprising a nucleotide sequence that encodes a VEGF-C polypeptide.
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> (See paragraph 41 of the published application (2004/0063656).)

Thus, the allegation that the claims involve use of inactive analogs is simply incorrect.

The Patent Office expressed a related concern that the claims may encompass "possibly millions" of VEGF-C species. This concern, even if true, does not support a written description rejection. The PTO's own written description training materials provide guidance that a single species of a novel polynucleotide (encoding a novel polypeptide) is sufficient to support a claim to a genus that includes, for example, 95% sequence variants, that easily reaches millions of species for protein-encoding genes of any significant length. As noted in the guidelines, and reflected in numerous issued patents in the recombinant DNA/protein arts, a cDNA (or amino acid) sequence coupled with a biological activity and assay for such activity is sufficient to provide written description of a genus of biologically active variants.

It is also important to remember that the current claims are directed to a *method of treatment* using a VEGF-C polynucleotide, and not to a VEGF-C polynucleotide *per se*. Alitalo et al. described the VEGF-C cDNA and amino acid sequences more than ten years ago and identified VEGF-C then as a ligand for VEGFR-3 (also known as Flt4 receptor tyrosine kinase). Since then, significant work has been performed characterizing those portions of the VEGF-C prepro-protein that are required for VEGFR-3 stimulation, and those portions that are not. The Patent and Trademark office has granted numerous patents to Alitalo et al. pertaining to such biologically active forms of VEGF-C, through which the Patent Office has repeatedly acknowledged that forms that vary from the exact wildtype

sequence can be made and tested and demonstrated to have VEGFR-3 activity without undue experimentation.

A number of the new and amended claims recite additional structure defining the VEGF-C gene therapy product to be used according to the invention. The description of VEGF-C herein (including pages 14-18 and 25-27 of the application and the citation to and incorporation by reference of PCT/US98/01973, published as WO 98/33917) provides more than adequate description to support the method claims of the invention-- especially in view of the fact that VEGF-C itself was the subject of the prior art, and is not being claimed as a DNA or protein product in this application.

C. VEGFR-3 alleles.

The claims were rejected in part because of the Patent Office's concern that Claims 37 and 38 "encompass a genus of VEGFR-3 alleles" that includes an enormous number of different species.

First, the Examiner cites no basis for this assertion. Specifically, the Examiner cites no evidence that there is an enormous number of mutant VEGFR-3 alleles associated with hereditary lymphedema.[1]

Second, even if there are an enormous number of mutant VEGFR-3 alleles, this fact does not support a rejection of the claims. The elected claims ARE NOT DIRECTED TO VEGFR-3 ALLELES (or to VEGFR-3 polypeptide variants). The claims are directed to a method of treating subjects with hereditary lymphedema. Because the written description requirement focuses on what is claimed, and because the claims under examination are not those directed to VEGFR-3 alleles, the rejection is misplaced.

In the context of what is claimed, the medical condition of hereditary lymphedema and its symptoms are well known. The application provides persuasive evidence that certain VEGFR-3 mutations are causative of hereditary lymphedema. Such evidence includes linkage evidence – the presence of the mutations in those family members with the hereditary lymphedema – and cell and molecular studies indicating that the mutant

proteins lack normal receptor signaling activity. The application also describes numerous techniques for identifying those hereditary lymphedema patients that have VEGFR-3 mutations:

> The "assaying" step of the invention may involve any techniques available for analyzing nucleic acid to determine its characteristics, including but not limited to well-known techniques such as single-strand conformation polymorphism analysis (SSCP) [Orita *et al., Proc Natl. Acad. Sci. USA, 86*: 2766-2770 (1989)]; heteroduplex analysis [White *et al., Genomics, 12*: 301-306 (1992)]; denaturing gradient gel electrophoresis analysis [Fischer *et al., Proc. Natl. Acad. Sci. USA, 80*: 1579-1583 (1983); and Riesner *et al., Electrophoresis, 10*: 377-389 (1989)]; DNA sequencing; RNase cleavage [Myers *et al., Science, 230*: 1242-1246 (1985)]; chemical cleavage of mismatch techniques [Rowley *et al., Genomics, 30*: 574-582 (1995); and Roberts *et al., Nucl. Acids Res., 25*: 3377-3378 (1997)]; restriction fragment length polymorphism analysis; single nucleotide primer extension analysis [Shumaker *et al., Hum. Mutat., 7*: 346-354 (1996); and Pastinen *et al., Genome Res., 7*: 606-614 (1997)]; 5' nuclease assays [Pease *et al., Proc. Natl. Acad. Sci. USA, 91*:5022-5026 (1994)]; DNA Microchip analysis [Ramsay, G., *Nature Biotechnology, 16*: 40-48 (1999); and Chee *et al.*, U.S. Patent No. 5,837,832]; and ligase chain reaction [Whiteley *et al.*, U.S. Patent No. 5,521,065]. [See generally, Schafer and Hawkins, *Nature Biotechnology, 16*: 33-39 (1998).] All of the foregoing documents are hereby incorporated by reference in their entirety.
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> (Specification at p. 6.)

The application further provides significant additional guidance for some of the preferred techniques for identifying VEGFR-3 mutations in lymphedema subjects, including techniques involving nucleic acid sequencing, polymerase chain reaction, hybridization assays, and combinations thereof. (See specification at pp. 7-9.)

The structure of human VEGFR-3 was known at the time that the patent application was filed. Nonetheless, the patent application provides additional descriptive support in the form of the relevant cDNA and deduced amino acid sequences for a healthy VEGFR-3 allele. See Figure 3 and SEQ ID NOs: 1 and 2. The application characterizes the

[1] Appended hereto are documents by Evans et al., J. Med. Genet. (2003), 40:697-703, Brice et al., J. Med. Genet. (2005) 42:98-102; Irrthum et al. (2003) and (2000); and Iljin et al. (2001), published after the effective filing date, identifying VEGFR-3 mutations in the families with primary congential lymphedema.

structure of VEGFR-3 genomic DNA in Example 4. (pp. 41-43.) The application also identifies the locations of VEGFR-3 hereditary lymphedema mutations for multiple families.

Finally, the application also describes and exemplifies a phosphorylation assay by which a person of ordinary skill can determine whether a newly discovered VEGFR-3 mutation affects VEGFR-3 phosphorylation. (See, e.g., Example 6, pp. 45-46.)

The Patent Office raised similar issues during prosecution of the method claims of parent patent no. 6,764,820, and eventually properly concluded that a generic method relating to detecting VEGFR-3 mutations was adequately described.

For all of these reasons, the aspects of the claimed method that relate to VEGFR-3 mutations in patients are adequately described.

D. *Fiers* and *Amgen* cases.

The Patent Office concludes the rejection by citing to the Federal Circuit's *Fiers* and *Amgen* decisions. As the Patent Office recognizes, these cases both involved the question of what constitutes an adequate written description of a novel DNA product invention. The present claims are not directed to DNA products, but rather to methods. Moreover, the cDNAs/proteins most relevant to the claimed invention – VEGF-C and VEGFR-3 – were described in the prior art. Thus, the *Fiers* and *Amgen* decisions are either irrelevant to this case because they involved different classes of invention and different facts, or to the extent they have any relevance, they support patentability because their criteria for written description are more than satisified by the present application.

For all of these reasons, the rejection for inadequate written description should be withdrawn.

III. The rejection alleging lack of enabling disclosure should be withdrawn.

At pages 8-13 of the Office action, the Patent Office alleged that the specification failed to enable the invention as claimed. The Patent Office acknowledges that the application is enabling for "ameliorating a symptom caused by hereditary lymphedema"

using certain specific VEGF-C nucleic acids, but feels that the invention is claimed too broadly. The Applicants respectfully traverse.

The Patent Office observes that the invention is in a field of science that the CAFC has characterized as unpredictable. This general characterization should not weigh against the current Applicants because, as the Examiner already has recognized, the Applicants have generated evidence that VEGF-C gene therapy can be effective for ameliorating lymphedema.

The Patent Office also bases its rejections in part on the fact that the claims embrace oral administration or administration to a location other than a location affected by lymphedema symptoms. These concerns are rendered moot by the current claim amendments, because the independent claims specify local administration.

The Patent Office's bases its rejection in part on the breadth of the claims as they relate to the VEGF-C gene therapy product to be used for therapy. However, this concern is misplaced, for reasons set forth in the preceding section.

Alitalo et al. described the VEGF-C cDNA and amino acid sequence more than ten years ago and identified VEGF-C then as a ligand for VEGFR-3 (also known as Flt4 receptor tyrosine kinase). Since then, significant work has been performed characterizing those portions of the VEGF-C prepro-protein that are required for VEGFR-3 stimulation, and those portions that are not. The Patent and Trademark office has granted numerous patents to Alitalo et al. pertaining to such biologically active forms of VEGF-C, through which the Patent Office has repeatedly acknowledged that forms that vary from the exact wildtype sequence can be made and tested and demonstrated to have VEGFR-3 activity without undue experimentation. A number of the new and amended claims recite additional structure defining the VEGF-C gene therapy product to be used according to the invention.

The Patent Office bases its rejection in part on the fact that the claims encompass treating hereditary lymphedema "caused by any VEGFR-3 mutant that has reduced ligand-mediated signaling." This allegation does not support a rejection, because the specification enables treating all such cases of hereditary lymphedema. In fact, the Patent Office has failed to provide any reasoning or evidence to the contrary. As the Patent Office acknowledges in the Office action, the Applicant has provided evidence that VEGF-C gene

therapy can overcome an inactivating, lymphedema-causing mutation in a VEGFR-3 allele. No reasoning or evidence has been provided for concluding that the therapy would be helpful for one inactivating mutation but not another. A theory explaining the therapeutic efficacy of VEGF-C gene therapy is that target lymphatic cells (in a lymphedema patient having a VEGFR-3 allele with an inactivating mutation) will have one wild type allele whose encoded protein forms functional wild type homodimers (with itself). Although the number of functional homodimers is reduced compared to a healthy individual with two wild type alleles, the VEGF-C gene therapy causes sufficient stimulation of the healthy homodimers to alleviate lymphedema symptoms. (See application at p. 27, lines 19-24.) Because the therapy is postulated to act on the wild type homodimers in patients with a lymphedema-causing mutant allele, the nature of the inactivating mutation in the mutant VEGFR-3 allele of the hereditary lymphedema patient should be immaterial.

The Patent Office bases its rejection in part on two articles that were cited to support the proposition that "direct delivery of the nucleic acid to the desired site of transfection is critical." Even if (for the sake of argument) the articles support this proposition in some circumstances, they do not support a rejection of the current claims. First, the amended claim set specifies local administration at a site of edema. The Patent Office has acknowledged in the Office action that the Applicants have established that local VEGF-C gene therapy can be successful for this indication.

Second, the therapeutic transgene in this case encodes a secreted growth factor, and secreted growth factors would be expected to contact the target cells (e.g., lymphatic endothelia) because secreted proteins would be expected to be present in lymphatic fluids. Thus, the articles cited by the Patent Office simply do not have an adequate nexus to the claimed invention, i.e., to treating VEGFR-3 hereditary lymphedema with a secreted growth factor gene therapy product.

Moreover, it is not clear that the articles even support the Patent Office's conclusions. For example, at page 405, Crystal comments, "Probably the most remarkable conclusion drawn from the human trials is that human gene transfer is indeed feasible . . . . [M]ost studies have shown that genes can be transferred to humans . . . and that all vector types function as intended. Taken together, the evidence is overwhelming, with successful

human gene transfer having been demonstrated in 28 ex vivo and 10 in vivo studies." Such conclusions do not support a rejection for lack of enablement.

While on the topic of "the state of the prior art," it is also important to recognize that the state of the art with respect to VEGF-C is sufficiently mature to support claims that are broad with respect to the transgene that is to be delivered. The Patent Office has already issued broad patents to, e.g., Alitalo et al., relating to the VEGF-C cDNA or encoded protein, and to fragments and variants that retain VEGFR-3 (Flt4) stimulating activity. More generally, the Patent Office's own written description guidelines and the body of gene/protein patents that the PTO has issued demonstrate the proper legal analysis. Namely, the important issue is NOT that a genus may encompass millions of minor sequence variants from a wildtype sequence. Rather, the issue is the recognition that a person of ordinary skill is able to make and successfully test such sequence variants to permit practice of the invention without undue experimentation. That is why the Patent Office routinely grants claims with permissive of sequence variation for gene/protein inventions.

In support of the rejection, the Examiner alleges that the application has no working examples. However, the Examiner acknowledges the significance of the *Chy* mouse studies published by Karkkainen et al. This mouse model was specified in prophetic Example 3 of the application.

The Applicants agree with the Patent Office that the level of skill in the field of the invention is considered to be high. This factor, too, supports a conclusion of enablement.

For all of the foregoing reasons, the rejection for lack of enabling disclosure was improper, and should be withdrawn.

IV. The rejections based upon alleged prior art should be withdrawn.

As explained in this section, all of the prior art rejections should be withdrawn.

A. The rejection of claims 12, 42, and 44-47 under Section 102(e).

The Patent Office rejected claims 12, 42, and 44-47 under 35 USC 102(e), alleging that the claims were anticipated by the teachings of Hu et al., U.S. Patent No. 6,040,157. The Applicants respectfully traverse.

At the outset, the Applicants reserve the right to demonstrate a date of invention prior to Hu et al.

Hu et al. cannot be said to teach a method for treating Milroy's disease. Rather, Hu et al. purports to teach a molecule that Hu et al. calls VEGF-2. In one paragraph in column 38, Hu et al. *suggests* that the VEGF2 *polypeptides* may be used to treat primary idiopathic lymphedemas, including Milroy's disease and Lymphedema praecox. However, this brief suggestion of polypeptide therapy is not supported by any teachings of whom to treat or how to treat. The closest example in the application is prophetic example 27, which pertains to treatment of secondary lymphedema following surgery, an indication previously taught by Alitalo et al. The single paragraph suggestion falls within a lengthy disclosure that also mentions in passing innumerable other alleged uses for VEGF2, including but not limited to angiogenesis; wound healing; growth of bone; treating deficiencies and disorders of the immune system; producing platelets, red blood cells, neutrophils, macrophages, B and T lymphocytes; treating at least 13 immune deficiency disorders, including HIV; stopping bleeding; clot formation; treating blood coagulation and platelet disorders; treating at least 25 autoimmune disorders; treating asthma, respiratory disorders, anaphylaxis; treating graft versus host disease; modulating inflammation; treating more that 25 viruses that cause numerous diseases; treating numerous bacterial and fungal infections; treating various parasitic agents; and other indications. (See, .e.g., columns 26-31.) A person of ordinary skill who read Hu et al. would not interpret Hu et al. to provide a teaching of how to treat any of the enormous list of diseases or conditions, including Milroy's disease, merely because the conditions are mentioned in a "wish list" in the application.

Additionally, the rejection has been rendered moot by amendments to claim 12 specifying that the patient has a lymphedema characterized by a VEGFR-3 mutation, and further specifying that the therapeutic composition be administered locally at a site of edema. Likewise, claim 37 has been rewritten in independent form and specifies a step of screening

for a VEGFR-3 mutation to identify the patient to treat. Such a screening step is neither disclosed nor suggested by Hu et al.

For these and other reasons, the rejection under Section 102(e) should be withdrawn.

B. The rejection of claims 12 and 48-49 under Section 103(a).

The Patent Office rejected claims 12 and 48-49 under Section 103(a), alleging that the subject matter of these claims was obvious in view of Hu et al. and Joukov et al., Reference C43. The Applicants respectfully traverse.

First, the alleged motivation to combine Hu et al. and Joukov et al. is questionable. The Patent Office points to Joukov et al.'s teaching about the specificity of the mutant VEGF-C for VEGFR-3, but the Patent Office fails to explain why Hu et al. would have motivated a person of ordinary skill to seek such a selective molecule.

Even if the teachings of the references are combined as suggested by the Patent Office, the Joukov article was cited solely for its teaching of a VEGFR-3 cysteine deletion mutant allegedly relevant to dependent claims 48-49. Joukov does not remedy the deficiencies in Hu et al. discussed above in the preceding section.

Finally, the Patent Office alleges that there would have been a reasonable expectation of success using the mutant VEGF-C to stimulate VEGFR-3. However, the claimed invention is not merely about stimulating VEGFR-3, but is about treating hereditary lymphedema in patients with a mutation in VEGFR-3. Nothing in either reference provides any basis for concluding that success is reasonably likely for treating such hereditary disease.

Thus, neither claim 12, nor new independent claim 37, nor any other claim is rendered obvious by the combination of Hu et al. and Joukov et al.

C. The rejection of claim 12, 37-38, and 40-41.

The Patent Office alleged that claims 12, 37-38, and 40-41 were obvious in view of Hu et al. and Kimak *et al.* (*American Journal of Human Genetics, 63(4)*, Abstract 180, A185 (1998); hereafter "Kimak *et al.*").

This rejection is improper because Kimak et al. is a report of work by inventors, and is not properly citable as prior art. Copies of two declarations from inventor Ferrell, originally filed in the parent application that has matured into U.S. Patent No. 6,764,820, are appended hereto for entry in this application. The declarations establish that Kimak and other articles should not be applied as prior art.

Because Kimak et al. is not properly citable as prior art, the rejection based in part on Kimak et al. should be withdrawn.

For the foregoing reasons, all of the rejections based on alleged prior art are improper, and should be withdrawn.

V. Conclusion

In view of the foregoing, the Applicants request reconsideration, withdrawal of all of the rejections, and allowance of all claims. The U.S. Patent and Trademark Office is authorized to charge any necessary unpaid fees due with this response to deposit account no. 13-2855, under order no. 28967/35255B.

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